Wilson disease (WD) is an autosomal-recessive disorder of hepatic copper metabolism that has tremendous variability in its presentation. Phenotypic diversity of the disease can lead to delayed diagnosis. We describe a case of WD in a 10-year-old boy presenting with 3 months of increasingly intense, spasmodic lower extremity muscle cramps. Physical examination revealed tenderness on calf palpation and dark flat lesions over his ankles, knees, and elbows. Initial testing revealed creatine kinase of 302 IU/L (normal 24–248 IU/L), hemoglobin of 8.9 g/dL (11.5–15.5 g/dL), aspartate aminotransferase of 114 IU/L (16–52 IU/L), alanine aminotransferase of 54 IU/L (2–30 IU/L), and myoglobinuria. Extensive evaluation of his myopathy, including MRI and muscle biopsy, was negative. Additional laboratory tests revealed a prothrombin time of 21.3 seconds (11.8–15.5 seconds), total bilirubin of 1.4 mg/dL (<1 mg/dL), albumin of 2.1 g/dL (3.1–4.6 g/dL), a reticulocyte percentage of 4.5% (0.5%–2.5%), a negative Coombs direct antibody test, ceruloplasmin of 3 mg/dL (21–51 mg/dL), and 24-h urine copper of 393 µg/24 h (15–60 µg/24 h). Liver biopsy showed patchy advanced fibrosis, mild inflammation, positive staining for copper, and a tissue copper concentration of 768 µg/g (10–35 µg/g). Brain MRI revealed symmetric intrinsic T1 shortening within bilateral basal ganglia. Trientene therapy was initiated for WD. Symptoms and laboratory abnormalities resolved and remain normal at 21 months’ follow-up. Musculoskeletal involvement in WD is uncommon and typically defined as bone demineralization, arthropathy, or hypokalemic muscle weakness. In patients with unexplained musculoskeletal symptoms and hepatic abnormalities, a diagnosis of WD should be considered and appropriate evaluation initiated. Pediatrics 2013;132:e1–e4
Wilson disease (WD), or progressive hepatolenticular degeneration, is a phenotypically variable autosomal-recessive disorder of hepatic copper metabolism. In this case report we describe a 10-year-old boy with WD who initially presented with muscle spasm and mildly elevated aminotransferases. This atypical presentation, and symptom resolution with chelation therapy, highlights the varied chief complaints of WD and the importance of screening tests to assist in early and accurate diagnosis.

**PATIENT PRESENTATION**

A 10-year-old boy presented with 3 months of increasingly intense spasmodic lower extremity muscle cramps. The cramps caused pain that radiated from his calves to his thighs, lower back, and right shoulder. The patient complained of fatigue and mild weakness but had no other systemic symptoms, including fever, arthritis, or change in cognitive function. Physical examination revealed tenderness on calf palpation and flat discolorations over his ankles, knees, and elbows. Initial testing revealed the following: creatine kinase of 302 IU/L (normal 24–248 IU/L), hemoglobin of 8.9 g/dL (11.5–15.5 g/dL), mean corpuscular volume of 74 fl, a red blood cell count of 4.2 × 10^12/μL (4.0–5.2 × 10^12/μL), an erythrocyte sedimentation rate of 44 mm/hour (0–20 mm/hour), aspartate aminotransferase of 114 IU/L (16–52 IU/L), alanine aminotransferase of 54 IU/L (2–30 IU/L), γ-glutamyltransferase of 47 IU/L (8–55 IU/L), alkaline phosphatase of 303 IU/L (90–300 IU/L), serum potassium of 3.8 mEq/L (3.7–5.5 mEq/L), serum uric acid of 3.4 mg/dL (2–7 mg/dL), serum CO2 of 22.6 mEq/L (23–30 mEq/L), urine pH of 5.5 (pH 5–8), glucosuria, and myoglobinuria. Family history was positive only for a sibling with autism spectrum disorder. The patient was taking no medications or supplements and reported no recent illness or injury.

Three months after initial presentation, laboratory tests revealed a prothrombin time of 21.3 seconds (11.8–15.5 seconds), total bilirubin of 1.4 mg/dL (<1 mg/dL), direct bilirubin of 0.5 mg/dL (<0.3 mg/dL), albumin of 2.1 g/dL (3.1–4.6 g/dL), reticulocyte percentage of 4.5% (0.5%–2.5%), and a negative Coombs direct antibody test. A ferritin level of 11 ng/mL (22–322 ng/mL) and a soluble transferrin receptor concentration of 132 nmol/L (8.8–28.1 ng/mL) indicated iron deficiency due to depletion through hyperactive erythropoiesis or secondary to hepatic disease that reduced the ability to store iron. Anemia with an elevated reticulocyte percentage, a red cell distribution width of 22% (12.5%–16%), and a mean corpuscular hemoglobin concentration of 28 g/dL (31–37 g/dL) suggested red blood cell hemolysis or loss with ineffective erythropoiesis. Serum amino acid (multiple elevations) and urine organic acid (tyrosyluria) screening was nonspecific. Intermittent minor elevations of creatine kinase, in the setting of myalgia and exercise intolerance, raised the possibility of metabolic myopathy. Serum levels of glucose 6 phosphate dehydrogenase, glutathione, phosphofructokinase, phosphoglycerate kinase, and triosephosphate isomerase were normal. Skin fibroblast culture for fatty acid oxidation studies revealed no abnormalities. Abdominal ultrasound with Doppler, lower extremity MRI, and muscle biopsy of the left vastus lateralis, including electron microscopy and extensive immunostaining, were normal. WD was not considered at this time, and ceruloplasmin was not sent. A skin biopsy of hyperpigmented lesions revealed a superficial peripheral perivascular lymphohistiocytic infiltrate. Bone marrow aspiration and biopsy showed moderately hypercellular marrow with focal necrosis, adequate megakaryopoiesis, and hypochromic microcytic anemia.

Over the next 3 months, the patient developed worsening muscle cramps and new bilateral nonpitting lower extremity edema. Brief, recurrent, severe cramps involving his forearms, hands, face, neck, anterior chest, and thighs occurred multiple times daily and limited activity. He remained ambulatory and functionally independent. Ophthalmologic examination revealed Kayser-Fleischer (KF) rings and sunflower cataracts. Serum ceruloplasmin was 3 mg/dL (21–51 mg/dL) and 24-h urine copper was 393 μg/24 h (15–60 μg/24 h). Liver biopsy showed patchy advanced fibrosis, mild inflammation, positive staining for copper, and an elevated tissue copper concentration of 768 μg/g (10–35 μg/g). Postoperatively, the patient developed rhabdomyolysis (elevation in creatine kinase [55 904 IU/L] and aldolase [15.6 μg/g]) that responded to symptomatic treatment. Rhodamine staining of the muscle biopsy was negative for copper deposition. Brain MRI with spectroscopy revealed symmetric intrinsic T1 shortening within bilateral basal ganglia (most prominently globus pallidus).

Selected images of the patient’s muscle biopsy (hematoxylin and eosin, rhodanine, cytochrome oxidase stains), liver biopsy (hematoxylin and eosin, rhodanine stains), KF rings, sunflower cataracts, brain MRI, and skin lesions are included in Supplemental Figures 1–5.

Therapy with trientine was initiated to treat WD. Muscle cramps, weakness, and most laboratory abnormalities resolved within 2 months of treatment. Prothrombin time normalized within 8 months. The patient remained symptom-free with normal aminotransferases, albumin, and prothrombin time at 21-month follow-up. The patient’s brother
was screened for WD due to his cognitive and behavioral disorder, with results of a ceruloplasmin concentration of 21 mg/dL (21–51 mg/dL) and a 24-h urine copper level of 10 μg/24 h (15–60 μg/24 h).

**DISCUSSION**

WD is a chronic disorder of copper metabolism with a worldwide average prevalence of 1 in 30,000. Despite identification of the sole mutated gene, ATP7B, and increased understanding of Wilson disease ATPase function in hepatocytes, associations between genetic mutation and clinical phenotype remain incompletely understood.1–3 Liver dysfunction in WD ranges from mild aminotransferase elevation to fulminant hepatic failure. Extrahepatic findings, with or without apparent liver injury, including neuropsychiatric, endocrine, hematologic, and renal abnormalities, result in a complex clinical spectrum that may lead to delayed or inaccurate diagnoses. Advanced hepatic and neurologic sequela of WD may be prevented by early disease identification and initiation of treatment.

Serum ceruloplasmin and basal 24-h urinary copper excretion, without the immediate need for genetic analysis, effectively identify most pediatric patients with WD.4,5 Notably, recommended pediatric screening thresholds of ceruloplasmin <20 mg/dL and 24-h urinary copper >40 μg/24 h may vary from laboratory normative values.5 The case presented had several features associated with WD that were eventually identified (liver involvement, KF rings, Coombs-negative hemolytic anemia, basal ganglia abnormalities), but the chief complaint of muscle spasm misdirected initial evaluation. Hyperpigmented anterior leg lesions are reported in WD, but they are characterized by increased basal layer melanin deposition that was not present in this case.6

Muscle spasm and rhabdomyolysis are not included as presenting symptoms of WD in textbooks or in national guidelines. Reports of musculoskeletal symptoms are mainly limited to bone demineralization, arthropathy,7 and hypokalemic muscle weakness.8,9 A case series abstract reported 28 WD patients, 19 with varied arthritis, and 8 with muscle cramps.10 Most of these patients were receiving the chelator penicillamine, a known cause of immunologically induced inflammatory myopathy.11 Musculoskeletal involvement in WD may be more common in those of Indian ethnicity, which did not apply to our patient. A study in Mumbai identified “osseomuscular” findings in 20 of 30 (66%) WD patients including 8 with recurrent joint pain initially dismissed as growing pains.12 Another study of WD patients in Bangalore found osseomuscular features in 37 of 282 (13%) patients, all with arthralgia, 6 with arthritis, and 22 with proximal weakness resembling myopathy.13 Neither myalgia nor rhabdomyolysis were described in patients of either study.

One case report in a 17-year-old male with WD included a history of muscle pain, weakness, KF rings, and decompensated cirrhosis at presentation.14 Initial muscle pain was not characterized, and recurrent acute rhabdomyolysis occurred subsequent to penicillamine therapy. Increased tissue copper on muscle biopsy suggested that at least a component of myopathy or rhabdomyolysis was related to WD and not to therapy. In our patient, muscle copper staining was negative and muscle parenchymal copper concentration was not measured.

Copper toxicity preferentially affects red blood cells, hepatocytes, and myocytes. Numerous reported cases of copper sulfate toxicity, both acute and chronic, manifest with rhabdomyolysis.15–17 Additionally, copper experimentally inhibits the Na+/K+ ATPase on cellular membranes and increases permeability.18 Copper is a cofactor of many enzymatic reactions, and there may be other undiscovered mechanisms of cellular injury.

Copper toxicity of skeletal muscle is the likely cause of muscle cramping and rhabdomyolysis in this case. Although staining of the patient’s muscle biopsy sample for tissue copper was negative, it is not clear that copper deposition is required for copper-induced myopathy. Cirrhosis, through an unknown mechanism, is also associated with muscle spasm. However, chelation therapy, which resolved symptoms in this case, has no effect on extent of cirrhosis. This patient never had significant serum electrolyte abnormalities (serum potassium of 3.5–4.6 mEq/L) that contributed to muscle weakness or injury. Centrally mediated muscle spasm and weakness are possible, but basal ganglia abnormalities could not account for rhabdomyolysis. This patient’s exacerbation of rhabdomyolysis subsequent to succinylcholine administration suggests that alternate paralytic agents should be considered in WD patients.

This case report identifies a phenotypic presentation of WD that includes muscle spasm and mild liver disease. Given the known mechanism of copper toxicity on myocytes, WD should be considered in the diagnosis of all children with unexplained musculoskeletal symptoms and hepatic abnormalities. A low threshold should exist to perform noninvasive screening of serum ceruloplasmin levels and basal 24-hour urinary copper excretion.

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Spasmodic Muscle Cramps and Weakness as Presenting Symptoms in Wilson Disease

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